Claims 1-20 are rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness on the basis that the phrase "said penetration enhancer" at lines 3-4 of claim 1 lacks antecedent basis. In response, Applicants respectfully point out that the phrase "said penetration enhancer" refers to the term "a penetration enhancer", which precedes the questioned term. Thus, it is believed that claim 1 is definite. As claims 3-20 depend directly or indirectly from claim 1, these claims are also definite.

Claim 13 has been amended to correct the typographical error pointed out by the Office Action.

Claim 15 is rejected as being indefinite under 35 U.S.C. §112, second paragraph, on separate grounds. The Office Action states that the "metes and bounds of the various components within formulation of claim 15, whose components are listed in lines 2-4, cannot be determined..." Applicants note, however, that claim 15 recites, "The formulation of claim 1, wherein said carrier particles are cationic." Thus, there are no "components...listed in lines 2-4" of claim 15. To the extent that the Office Action may have intended to refer to claim 13, Applicants respectfully assert that the claim language makes it clear that the formulation comprises any one of the listed components, or any combination of the same. To the extent that the Office Action may have intended to refer to claim 16, that claim has been amended to recite "lysine-ethyl ester *or* arginine ethyl-ester" to comply with accepted Markush Groups language. Further, amended claim 16 is fully supported by the specification at, for example, page 3, beginning with the third line from the bottom, to the first line of page 4.

Claim 18 has been amended to correct the typographical error pointed out by the Office Action.

In view of the preceding discussion, Applicants respectfully assert that claims 1-20 comply with 35 U.S.C. §112, second paragraph. Withdrawal of these rejections is therefore respectfully requested.

Claims 1, 2, 4-9, 11, 13-15 and 17-20 are rejected under 35 U.S.C. §102(e) for alleged anticipation by U.S. Patent No. 6,458,383 B2 to Chen et al ("Chen et al."). The cancellation of claim 2 rendered the rejection of that claim moot. Applicants traverse the rejections of claims 1, 4-9, 11, 13-15 and 17-20 and request reconsideration of the same.

It will be appreciated that an anticipating reference must disclose all the features of a claim. Claim 1 recites a delayed release oral formulation for enhanced intestinal oligonucleotide absorption comprising a *first* population of carrier *particles*, and a *second* population of carrier *particles*. Accordingly, claim 1 includes the features of a *first* and a *second* population of carrier *particles*.

Chen et al. generally discloses a dosage form comprising a composition of: (a) a therapeutically effective amount of low molecular weight heparin; (b) a bile salt or bile acid; (c) at least one surfactant selected from hydrophilic surfactants, lipophilic surfactants, and mixtures thereof; and a means for delaying release of the composition from the dosage form following oral administration. Furthermore, Chen et al. generally discloses how the "amounts of the bile salt or bile acid and the surfactant(s) can be readily determined by the average particle size of the aqueous dispersion form from the composition upon dilution in an aqueous medium" and how the particle size may be determined. (Col. 17, line 48, to Col. 18, line 7). Chen et al. further provides working examples that include the use of particles, e.g., Examples 19 and 22. However, Chen et al. does not disclose, teach or even suggest a formulation comprising a *first* and a *second* population of carrier *particles*, much less a *first* and a *second* population of carrier *particles* having the features recited in claim 1. Thus, Chen et al. does not anticipate claim 1.

Claims 4-9, 11, 13-15 and 17-20 depend directly or indirectly from claim 1. Therefore, the formulations (claims 4-9, 11 and 13-15) and methods (17-20) of these claims include a first and a second population of carriers. As discussed above, Chen et al. does not disclose a first and a second population of carrier particles as recited in each of claims 4-9, 11, 13-15 and 17-20. Accordingly, Chen et al. does not anticipate claims 4-9, 11, 13-15 and 17-20.

Claims 1-3, 15 and 16 are rejected under 35 U.S.C. §103(a) for alleged obviousness over Chen et al. in view of U.S. Patent No. 6,309,853 B1 to Friedman et al. ("Friedman et al.") and U.S. Patent No. 5,876,742 to Cochrum et al. ("Cochrum et al."). The cancellation of claim 2 rendered the rejection of claim 2 moot. Applicants traverse the rejections of claims 1, 3, 15 and 16 and request reconsideration of the same.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Office to provide a reason why one of ordinary skill in the art would have been led to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation **must** stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and **not** from applicants' disclosure. See for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent applicant has done.

(citations omitted; emphasis added). Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to combine particular teachings of the cited references and achieve the claimed invention.

The Office Action alleges that it would have been obvious at the time the invention was made for one of ordinary skill in the art to "utilize compositions (for delayed release of a drug) comprising a first population of particles...and a second population of particles...because Chen et al teach first and second populations of particles for delayed drug release in a mammal..." The Office Action further alleges that one of ordinary skill

> would have been motivated to use slow release particles for enhanced delivery of antisense oligonucleotides within the digestive tract and that the delivery of antisense oligonucleotides to the digestive tract would be enhanced using delayed release particles described in either Chen et al, Friedman et al or Cochrum et al.

(Office Action at page 6).

However, as discussed above, and contrary to the assertion of the Office Action, Chen et al. does not disclose, teach or even suggest a formulation comprising a *first* and a *second* population of carrier *particles*, much less a *first* population of carrier particles having a penetration enhancer released at a first location in the intestine, and a *second* population of carrier *particles* having the penetration enhancer released at a second location in the intestine, whereby the absorption of the oligonucleotide is enhanced at the second location. Although Chen et al. states at Col. 7, lines 55-57 that "[a]fter the dosage form reaches the intended release site, there may or may not be a further mechanism controlling the release of the composition from the dosage form[,]" this is a generalized, vague statement that does not teach the present invention. Nothing whatsoever in Chen et al. teaches or suggests that the "mechanism controlling the release" is a formulation comprising a first and a second population of carrier particles, or that a penetration enhancer is released downstream from the first location, or that the absorption of the oligonucleotide is increased at the second location.

Friedman et al. and Cochrum et al. do not cure the deficiencies of Chen et al. Friedman et al. generally discloses nucleotides sequences corresponding to murine and human OB gene that demonstrate the ability to participate in the control of mammalian body weight. Friedman et al. further states that antisense oligonucleotides directed to this gene may be administered for therapeutic treatments (Col. 47, lines 40-45). Friedman further discloses that the therapeutics can be included in a "formulation as fine multiparticulates in the form of granules or pellets of particle size" (Col. 44, lines 34-36), and the formulation may have delayed release effects. (Col. 45, lines 38-48).

Cochrum et al. discloses coating materials (e.g., poly L-lysine and alginate) for tissue transplant, wherein the coating materials prevent the destruction of the tissue transplant by the host's immune system. Furthermore, Cochrum et al. discloses that the coating is permeable to allow a free diffusion of nutrients to the transplant. (Col. 1, lines 50-55).

Neither Friedman et al. nor Cochrum et al., individually or combined with Chen et al., disclose, teach or suggest a formulation comprising a first and a second population of

carrier particles (claim 1), wherein the oligonucleotide is an antisense oligonucleotide (claim 3), wherein the carrier particles are cationic (claim 15), or wherein the carrier particle comprise a complex of poly-L-lysine and alginate (claim 16). Thus, the recited art, even combined, simply fails to produce Applicants' claimed invention.

As discussed above, for a rejection under 35 U.S.C. §103 to stand, the combination of the cited art must teach or suggest the claimed invention. In the present instance, the Office Action has not provided any legally sufficient motivation to modify the teachings of the cited art to achieve the inventions of the claims. There simply is no teaching or suggestion in the cited art, or in the combination thereof, to employ two populations of particles having the composition of the claims. Indeed, the only suggestion of the use of two such populations of particles is provided by Applicants disclosure, which is not available as prior art. Thus, Applicants respectfully assert that the present claims are not obvious in view of the cited art. Accordingly, Applicants respectfully withdrawal of this rejection.

Claims 1, 2, 6, 10 and 12 are rejected under 35 U.S.C. §103(a) for alleged obviousness over Chen et al. in view of WO 85/02092 to Robinson ("Robinson"). The cancellation of claim 2 rendered the rejection of claim 2 moot. Applicants traverse the rejections of claims 1, 6, 10 and 12 and request reconsideration of the same.

The Office Action asserts that it would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to combine Chen et al. and Robinson to arrive at the inventions recited in the rejected claims.

Chen et al. is discussed above. Robinson discloses a composition comprising a bioadhesive (as a controlled release agent) and a treating agent.

As discussed above, there is no teaching in Chen et al. that would provide a "motivational force" that would "impel" one of ordinary skill to employ a formulation comprising a first and a second population of carrier particles, much less a first population of carrier particles having a penetration enhancer released at a first location in the intestine, and a second population of carrier particles having the penetration enhancer released at a second location in the intestine.

Robinson does not cure the deficiencies of Chen et al. Robison, alone or combined with Chen et al., do not disclose, teach or even suggest a formulation comprising a first and a second population of carrier particles comprising penetration enhancers that are released at a first and a second location, respectively, (claim 1), wherein the penetration enhancer is selected from the group consisting of a fatty acid, bile salt, chelating agent and non-chelating non-surfactant (claim 6), wherein the penetration enhancer is a non-chelating non-surfactant an unsaturated cyclic urea, 1-alkyl-alkanone, 1-alkenylazacycloalkanone, steroid anti-inflammatory agent or mixtures thereof (claim 10), and wherein the carrier particles are biadhesive (claim 12). Because the combination of the Chen et al. and the Robinson references would not produce or suggest the inventions of the claims, Applicants respectfully assert that the claims are not obvious in view of these references. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. §103.

The claims presently pending are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned representative at (215) 665-2158 to clarify any unresolved issues raised by this response.

Respectfully submitted,

Quan L. Nguyen
Registration No. 46,957

Date: July 18, 2003

COZEN O'CONNOR
1900 Market Street
Philadelphia, PA 19103
(215) 665-2158 (phone)
(215) 701-2057 (fax)

Doc. No. 1879487 v1